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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/998,923	12/03/2001	Laura P. Hale	1579-628	4251

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EXAMINER	
UNGAR, SUSAN NMN	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 04/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/998,923	HALE ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *24 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,4-6 and 8-19* is/are pending in the application.

4a) Of the above claim(s) *8-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1 and 4-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/27/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. The Amendment filed January 24, 2005 in response to the Office Action of July 23, 2004 is acknowledged and has been entered. Claims 2-3 and 7 have been canceled, claims 1 and 6 have been amended. Claims 1, 4-6 are currently under prosecution.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

New Grounds of Rejection

Claim Rejections - 35 USC 103

3. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.
>
> Patentability shall not be negatived by the manner in which the invention was made.Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

4. Claims 1, 4 and 5 are rejected under 35 U.S.C. § 103 as being unpatentable over Bundred et al, of record, in view of Poortmann et al of record.

The claims are drawn to a method of screening for cancer in a test mammal comprising assaying for the level of ZAG present in a serum sample from said test mammal and comparing that level to a serum control from a mammal of the same species, wherein an elevated level of ZAG in the serum sample from the test mammal relative to said control is indicative of the presence of cancer (claim 1), wherein ZAG is immunoassayed (claim 4), wherein the assay is an antigen capture assay (claim 5).

Bundred et al teach as set forth previously, but does not teach the assay in serum.

Poortmann et al teach as set forth previously that is that expressed ZAG is found in serum fluids including plasma and teaches conventional antigen capture immunoassay for ZAG, wherein both the test sample (after exercise) and the control sample were taken from mammals of the same species and assayed by the same assay method (pg 808-809).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the conventional serum immunoassay of Poortmann et al for the identification/screening of invasive breast carcinoma immunoassay of Bundred et al wherein it was found that ZAG is overexpressed in 50% of invasive breast carcinomas because it was known that ZAG is a soluble protein found in all body fluids and in particular Poortman et al specifically teach that ZAG was found in plasma. Since ZAG is known as a secreted protein, it would be expected that overexpression of ZAG in the tumor would be associated with increased secreted protein in plasma. Thus one would have a reasonable

expectation of success in screening for invasive breast carcinoma, not only in the patients disclosed in the method of Bundred et al, but also in patients suspected of having invasive breast carcinoma. One would have been motivated to screen the serum of a patient suspected of having invasive breast carcinoma in order to quickly and inexpensively determine the necessity to do additional, more invasive testing for breast carcinoma.

5. Claim 1, 4 and 5 is rejected under 35 U.S.C. § 103 as being unpatentable over Lopez-Otin et al, of record, in view of Poortmann et al of record.

The claim is drawn to a method of diagnosing cancer in a test mammal comprising assaying for the level of ZAG present in a serum sample from said test mammal and comparing that level to a serum control from a mammal of the same species, wherein an elevated level of ZAG in the serum sample from the test mammal relative to said control is indicative of the presence of cancer (claim 1), wherein ZAG is immunoassayed (claim 4), wherein the assay is an antigen capture assay (claim 5).

Lopez-Otin et al teaches as set forth previously, but does not teach the assay in serum.

Poortmann et al teach as set forth previously that is that expressed ZAG is found in serum fluids including plasma and teaches conventional antigen capture immunoassay for ZAG wherein both the test sample (after exercise) and the control sample were taken from mammals of the same species and assayed by the same assay method (pg 808-809).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the conventional serum antigen capture immunoassay of Poortmann et al for the identification/screening of

mammary tumor immunoassay of Lopez-Otin et al wherein it was found that mammary tumors produce and secrete appreciable amounts of ZAG because it was known that ZAG is a soluble protein found in all body fluids and in particular Poortman et al specifically teach that ZAG was found in plasma Since ZAG is known as a secreted protein, it would be expected that overexpression of ZAG in the tumor would be associated with increased secreted protein in plasma. Thus one would have a reasonable expectation of success in screening for invasive breast carcinoma, not only in the patients disclosed in the method of Lopez-Ortin, but also in patients suspected of having mammary tumors. One would have been motivated to screen the serum of a patient suspected of having mammary tumors in order to quickly and inexpensively determine the necessity to do additional, more invasive testing for breast carcinoma.

Claim Rejections - 35 USC 112

6. Claims 1, 4-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening for cancer in a test mammal suspected of having cancer comprising the claimed assay, does not reasonably provide enablement for a method of screening for cancer in a test mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a method for diagnosing cancer in a test mammal comprising assaying for the level of ZAG present in a biological sample from said test mammal and comparing that level to a control sample wherein an elevated level of ZAG in the biological sample from said test mammal relative to said control is indicative of the presence of a tumor.

The specification teaches that ZAG concentrations can be used to screen for/ diagnose a variety of tumor types including prostate, breast, colon, squamous cell and pancreatic cancers. In particular, the specification teaches that high levels of ZAG are present in prostate cancer serum, whereas lower levels are present in BPH serum or the serum of normal controls (see p. 9). It appears also that patients with enlarged normal prostate present with high levels of ZAG (p. 10, lines 105). Todorov et al, Cancer Res. 1998, 58:2353-2358 (IDS item) quantitated ZAG production by MAC16 colon adenocarcinoma tumors wherein MAC16 produced large quantities of ZAG when compared to normal controls (p. 3, lines 1-17).

One cannot extrapolate the teaching of the specification to the enablement of the claims because it is well known in the art that ZAG overexpression is associated with cachexia , a physical decrease in carcass lipid seen in a variety of chronic and severe diseases. These diseases include cancer, Aids, sleeping sickness, schistsomiasis and tuberculosis (Kennedy et al, 7th International Symposium on Schistosomiasis, Abstract, of record). In particular, Taber's Cyclopedic Medical Dictionary, 1989, F.A. Davis, Philadelphia, p. 1649 defines "screening" as "The testing, usually using one diagnostic procedure including laboratory studies, of large groups of people to determine the presence of a particular disease." Clearly, given the teaching above, one would not have a reasonable expectation of success in screening for a particular disease, cancer, in the broadly claimed patient population, by assaying for ZAG concentrations in serum.

Further, ZAG over-production from tumors has been associated with lipolysis and cachexia in advanced cancers (see Wang et al, 3rd Annual Western Canadian Structural Biology Workshop, Frontiers in Structural Biology, November

20-23, 2003, Banff, Alberta, Canada, see Abstract of record). During cachexia, ZAG production is increased 10-fold (see World Health News, November 7, 2003, abstract, Obesity Pill Near, of record). Interestingly, Todorov et al, of record, specifically teach that cancer patients with weight loss showed urinary excretion of ZAG while cancer patients without weight loss or normal subjects did not (see abstract). Given the above, it is clear that cachexia is associated with the overexpression of ZAG and that the biological fluid increases of ZAG concentration found in cancer patients is not associated with the cancer *per se*, but rather is associated with the cachexia, which is a concomitant characteristic presented by some of the patients suffering from a variety of chronic and severe diseases. Given the above it cannot be predicted and would not be expected, in the absence of guidance to a particular patient population that an increase in ZAG in plasma or any other biological fluid could be used to indicate the presence of cancer, as currently claimed because a positive screening test would be as likely to be indicative of AIDS, sleeping sickness, schistsomiasis or tuberculosis or any other diseases associated with cachexia as it would be indicative of cancer. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the claimed invention could be used with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

Applicant's arguments are relevant to the newly imposed rejection.

Applicant argues that the claims have been amended to more clearly indicate that the instant invention is a screening method, that is, it is a method that can be

used to identify a test mammal that is at an increased likelihood of having cancer which is similar in nature to the well known prostate cancer screening methods based on elevated levels of PSA. Although not a definitive diagnosis of cancer provided by biopsy, it nonetheless represents an invaluable diagnostic tool, likewise the method of the instant claims.

The argument has been considered but has not been found persuasive because contrary to Applicant's arguments, elevated levels of ZAG are not similar to elevated levels of PSA for screening purposes. PSA is well known in the art as a conventional marker for prostate diseases. Given its elevation, one could predictably screen a patient for prostate cancer, BPH or prostatitus with a reasonable expectation of success in identifying a patient with a prostate condition. However ZAG, unlike PSA, which is elevated in disorders of the prostate, is elevated in a wide variety of chronic and severe diseases that present with increased concentrations of ZAG in plasma or any other serum fluid. Given an increase in ZAG concentrations, one would not know how to use the claimed invention for the reasons set forth above.

Further, Applicant is arguing limitations not recited in the claims as currently constituted because the claims are not drawn to identification of a test mammal that is at increased likelihood of having cancer. The arguments have been considered, have not been found persuasive and the rejection is maintained.

7. Claims 1, 4-6 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of ZAG level immunoassay for both test animal and control done using the same technique has no clear support in the specification and the claims as originally filed. In the response filed January 24, Applicant states that claim 1 was

amended to make explicit that which is believe to be implicit in the term control. However, the suggested implicit support is not found persuasive because a review of the specification revealed that there is no teaching or guidance that would suggest that the newly added limitation was contemplated at the time the invention was made. The subject matter claimed in claims 1, 4-6 broadens the scope of the invention as originally disclosed in the specification.

Specification

8. Objection to the specification, page 3, section 1 of the paper mailed January 24, 2005 is maintained because Applicant has not amended the specification to reflect the status of the parent application.

9. All other objections and rejections imposed in the paper mailed July 23, 2004 are hereby withdrawn.

10. No claims allowed.

11. This action is a **final rejection** and is intended to close the prosecution of this application. Applicant's reply under 37 CFR 1.113 to this action is limited either to an appeal to the Board of Patent Appeals and Interferences or to an amendment complying with the requirements set forth below.

If applicant should desire to appeal any rejection made by the examiner, a Notice of Appeal must be filed within the period for reply identifying the rejected claim or claims appealed. The Notice of Appeal must be accompanied by the required appeal fee.

If applicant should desire to file an amendment, entry of a proposed amendment after final rejection cannot be made as a matter of right unless it merely cancels claims or complies with a formal requirement made earlier. Amendments touching the merits of the application which otherwise might not be

proper may be admitted upon a showing a good and sufficient reasons why they are necessary and why they were not presented earlier.

A reply under 37 CFR 1.113 to a final rejection must include the appeal from, or cancellation of, each rejected claim. The filing of an amendment after final rejection, whether or not it is entered, does not stop the running of the statutory period for reply to the final rejection unless the examiner holds the claims to be in condition for allowance. Accordingly, if a Notice of Appeal has not been filed properly within the period for reply, or any extension of this period obtained under either 37 CFR 1.136(a) or (b), the application will become abandoned.

12. Applicant's amendments necessitated the new grounds of rejection. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R.

1.136(a).

> A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday

through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at 571-272-0787. The fax phone number for this Art Unit is (571) 273-8300.

Susan Ungar, PhD
Primary Patent Examiner
March 28, 2005